II. REMARKS

A. Status of the Claims

This is in Response to the Non-Final Office Action dated September 1, 2009. A petition for three-month extension of time and corresponding fee accompanies this Amendment.

Claim 9 has been amended without prejudice to incorporate the limitations recited in claims 23 and 24 of the present invention. Claims 23 and 24 are cancelled without prejudice in the present paper. Claim 9 has also been amended to add "which is not expressed in normal liver". Support for the aforementioned amendment to claim 9 can be found in pages 42-43 of the specification as filed under the subtitle of "Expression Analysis of human GPC3 mRNA using GeneChip."

Claims 1-8 and 10-22 were previously canceled without prejudice. Claims 23 and 24 are cancelled without prejudice in the present paper.

New claims 30-41 were added for consideration which are directed to an antibody specified by the sequence of its CDRs. Support for new claims 30 to 41 can be found in the present specification as filed, for example, from page 16, line 1 to page 20, line 20, and Example 4, as well as in the sequence listing.

After claim amendments, cancellations and additions herein, claims 9 and 25-41 will be pending in this application.

It is respectfully submitted that no new matter is being introduced in this amendment.

B. Claim Rejections- 35 U.S.C. § 103

In the Office Action mailed on September 1, 2009, the rejection of claims 9 and 23 to 29 under 35 U.S.C. 103(a) as being obvious over Lage et al. (Virchows Arch 2001 438:567-573), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of

Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) were maintained.

In the Office Action, the Examiner alleges *inter alia* that a person skilled in the art at the time the invention was made would have humanized the monoclonal antibody of Lage et al. using the methods of Steplewski et al., in order to overcome the problems involved in using mouse monoclonal antibodies in human therapy.

In addition, the Examiner alleges that Steplewski et al. teach that humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes, and Dillman et al. teach that humanized antibodies exhibit complement-mediated cytotoxicity. Thus, one would have been motivated to humanize the monoclonal antibody disclosed in Lage et al., given that GPC3 is highly expressed in HCC, given that HepG2 cells express GPC3 on their cell surface at elevated levels, and given the importance of developing new cancer therapeutics.

The Applicant respectfully disagrees with the Examiner position. The mouse antibody CQ17-1A with a humanized modification originally has a high binding activity toward U-937 cells (see Steplewski et al., page 4853, left column, 5th paragraph "Binding of Chimeric mAbs to FcR" and Fig. 1). On the contrary, the Be-F4 antibody of Lage et al. binds more tightly to the normal liver tissue than to hepatic cancer cells. One could never have been motivated to obtain a humanized antibody having desired properties to meet the goal of developing a new cancer therapy with a reasonable expectation of success by effecting humanized modification starting from the Be-F4 antibody having such a binding property.

However, in order to expedite the prosecution of the present application, independent claim 9 of the present application has been amended without prejudice to add the feature of the antibody of the present invention "which is not expressed in normal liver." Applicants respectfully submit that the amended claims of the present invention further distinguish the present invention from the Be-F4 antibody disclosed in Lage et al.

"An antibody against a peptide consisting of amino acid residues 375-580 of GPC3 as set forth in SEQ ID NO: 4 which is not expressed in normal liver" of the present invention as claimed in the amended Claim 9 is not disclosed nor suggested in Lage et al. The antibody of the present invention and the Be-F4 antibody disclosed in Lage et al. show opposite binding properties. Namely, the former is an antibody against the peptide 375-580 of GPC3 which is not expressed in normal liver tissue, and the latter binds more tightly to normal liver tissue than liver cancer cells. A person skilled in the art would have never been motivated to combine Lage et al. with Steplewski et al., further with Dillman et al., further with Mast et al., and further with Midorikawa et al. Also a person skilled in the art would have never had a reasonable expectation of success in arriving at the present invention as claimed in Claim 9 which has an opposite binding property from the antibody Be-F4 which binds more tightly to normal liver tissue than hepatic cancer cells.

In addition, the disclosure of Dillman et al. merely provides a general guidance of humanized antibodies but fails to provide a clear teaching or implication to direct someone toward the feature of the present invention. Mast et al. and Midorikawa et al. do not provide clear teaching or implication about the feature of the present invention "antibody against a peptide consisting of amino acid residues 375-580 of GPC3 as set forth in SEO ID NO:4" as recited in claim 9 of the present invention.

Accordingly, a person skilled in the art would have never had a reasonable expectation of success to achieve the present invention as claimed in Claim 9 which has an opposite binding property from the antibody Be-F4 which binds more tightly to normal liver tissue than hepatic cancer cells. In conclusion, a person skilled in the art could not have conceived of the present invention based on the combination of the cited references.

The rejection of claims 23 and 24 is now moot as claims 23 and 24 have been cancelled without prejudice in the present paper. Claims 25 to 29 depend directly either directly or indirectly from independent claim 9 which is discussed above.

For the foregoing reasons, withdrawal of the rejection of claims 9 and 23 to 29 under 35 U.S.C. 103(a) is respectfully requested.

In the Office Action mailed on September 1, 2009, the rejection of claims 9 and 23 to 29 under 35 U.S.C. 103(a) as being obvious over Filmus et al. (US Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85:4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327:577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) were maintained.

In the Office Action, the Examiner alleges *inter alia* that a person skilled in the art at the time the invention was made would have humanized the monoclonal antibody 1G12 disclosed in Filmus et al. using the methods of Steplewski et al, in order to overcome the problems involved in using mouse monoclonal antibodies in human therapy.

In addition, the Examiner alleges *inter alia* that Steplewski et al. teach that humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes, and Dillman et al. teach that humanized antibodies exhibit complement-mediated cytotoxicity. Thus, one would have been motivated to humanize the monoclonal antibody disclosed in Filmus et al., given that GPC3 is highly expressed in HCC, given that HepG2 cells express GPC3 on their cell surface at elevated levels, and given the importance of developing new cancer therapeutics.

The Examiner mentioned in the office action that the claims are not drawn to antibodies with inherent cytotoxic activity (page 9, line 17). Although the Applicants do agree with the Examiner's position, the Applicants have amended Claim 9 without prejudice to add the feature "having ADCC or CDC activity", in order to accelerate the examination.

As the Applicant asserted in the response to the previous office action, it was well known in the art that the IG12 antibody disclosed in Filmus et al. did not exhibit cytotoxicity (e.g., ADCC activity and CDC activity) in unconjugated form. Accordingly, a person skilled in the art

would never had a reasonable expectation of success in obtaining an antibody with ADCC activity or CDC activity as defined in the amended Claim 9 based on the 1 G12 antibody disclosed in Filmus et al. which clearly does not exhibit ADCC activity or CDC activity, even in view of Steplewski et al, further in view of Dillman et al., further in view of Mast et al. and Midorikawa et al.

In conclusion, a person skilled in the art could not have conceived of the present invention based on the combination of the cited references.

The rejection of claims 23 and 24 is now moot as claims 23 and 24 have been cancelled without prejudice in the present paper. Claims 25 to 29 depend directly either directly or indirectly from independent claim 9 which is discussed above.

For the foregoing reasons, withdrawal of the rejection of claims 9 and 23 to 29 under 35 U.S.C. 103(a) as being obvious over Filmus et al. (US Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85:4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327:577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) is respectfully requested.

Double Patenting Rejectios

In the Office Action, claims 9 and 23 to 29 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 6, 7, 16, 21, 22, 29, 32, 34, 38, 39, 41, and 43 to 50 over copending U.S. Patent Application No. 10/583,795.

Applicants acknowledge the rejection and submit that filing of a terminal disclaimer will be considered upon indication that the current claims or the pending claims of U.S. Patent Application No. 10/583,795 are otherwise allowable.

Conclusion

Reconsideration of the present application is respectfully requested. If the Examiner has any questions or concerns regarding this response and amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number set forth below.

Respectfully submitted,
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